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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| PRIEBE, SCOTT DAVID | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 07/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/723,272 | HINTON, GOLDEN S. | |
| | Examiner | Art Unit | |
| | Scott D. Priebe, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20031126.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Specification*

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 9, 13 and 18 recite "subcutaneous", "intra-muscular", and "intra-abdominal". There is no antecedent basis in the specification for these terms.

### *Claim Objections*

Claims 3 and 5-7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The method of claim 1 appears to involve administration of bacteria specifically, whereas dependent claims 3 and 7 appears to expand the method to delivery of other microorganisms (claim 3), which would include viruses, yeast, protozoans, etc., and naked DNA/RNA or DNA/RNA enclosed by a cellular membrane or artificial enclosure (claim 7). This subject matter is outside the scope of claim 1, which is limited to delivery of bacteria (or bacterial DNA/RNA).

Claim 4 requires introducing the bacteria by intravenous infusion. Claim 5 allows the method of introducing the bacteria to include other methods of introduction outside the scope set forth in claim 4.

Claim 1 is limited to the action of antibiotics to "spill" the DNA/RNA into the bloodstream. Claim 6 allows the spillage (rupture) to be induced by means outside the scope of claim 1.

Claims 1, 7, 8, 10, 12-14, 16, 18, and 19 are objected to because of the following informalities. Recitation of DNA/RNA is improper grammar. The "/" should be replaced with the appropriate connective, e.g. "or", "and". Appropriate correction is required.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-21 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility.

Claims 1-21 are directed to a method of treating a patient having cells containing damaged DNA, such as cancer cells, by causing release of DNA and RNA from microorganisms, such as bacteria, introduced into the patients bloodstream, wherein the DNA and RNA of the microorganism are utilized by "repair enzymes" to repair the damaged DNA in the cells of the patient. In so far as the claims require the particular mechanism of action of repair of damage, i.e. mutations, in the DNA of a patient's cells, the claimed method is inoperative. The hypothesis that DNA and RNA of bacteria or another microorganism could be used by repair enzymes in the patient's cells to repair damage DNA in the patient's cells is contrary to what is known about mechanisms of DNA repair and correction of mutations.

There are several reasons why the proposed mechanism of action of the method is physically impossible. The claims refer to "broken cancer cell DNA" and "damaged RNA/DNA" in cancer cells and other cells. The specification (page 3, line 1-4) refers to replacing damaged or broken DNA in a cancer cell with DNA from bacteria. Consequently, it is presumed that the claims refer to repairing mutations in cancer cells by recombination, rather than repairing physical damage such as UV photoproducts, double-strand breaks, damaged nucleotides and various DNA adducts. Mutations are not damage *per se*, except perhaps from a teleological viewpoint, but often are the result of damage that has been repaired incorrectly, but may also result from non-homologous or illegitimate recombination. In order to replace mutations in cancer cell DNA, the donor DNA must be first be capable of providing the correct nucleotide sequence to replace the mutated DNA, i.e. the donor DNA must be homologous (identical or nearly identical in sequence) to the mutant sequence in the tumor cell (Lewin, Genes VI, Oxford Univ. Press, New York, 1997, pages 531-534). This criterion cannot be met by bacterial DNA, which is entirely different in nucleotide sequence from that of man, for example. With respect to bacterial RNA, RNA in vertebrate cells is not a substrate for repair of DNA either by repair enzymes or homologous recombination. These are distinct biomolecules with vastly different roles in a cell. See Sancar et al. (Annu. Rev. Biochem. 73: 39-85, 2004), which is a review on DNA repair in mammals, and Lewin *supra* at pages 645-648 and 687, which shows the great disparity in both size and complexity between bacterial and mammalian genomes.

Furthermore, many of the mutations in present in cancerous cells cannot be "repaired" by any known mechanism due to their extensive nature even by homologous DNA. The most common genetic abnormality in cancer cells is aneuploidy, the loss or duplication of one or more

chromosomes. Aneuploidy cannot be repaired by repair enzymes in cells. The most prevalent mutations in cancer cells result from gross chromosomal rearrangements, such as deletions, inversions, translocations and amplifications, rather than point mutations. See Lengauer et al. (Nature 396: 643-649, Dec. 1998), which summarizes the various types of genetic alterations found in cancer cells. Also see Silverman et al. (Cancer 80(12): 2285-2295, Dec. 1997, at pages 2286, 2292); Kamb et al. (Science 264: 436-440, April 1994, at page 437); and Saadatmandi et al. (Cancer Gene Ther. 9(10): 830-839, Oct. 2002). In other words, substantial regions of chromosomes are simply lost or are moved to different chromosomes or different locations within the same chromosome. Regardless of the nature of lesions of these types, normal human DNA, for example, would not be able to pair with the mutated DNA involved with these gross genetic alterations in a cancer cell such that homologous recombination could occur to "repair" the mutation.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, and 12-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete. It is directed to a method; however no active process steps are recited. The claims simple recites what happens as a consequence of whatever the method

actually is. It is also unclear from the sentence structure whether the bacteria are killed by antibiotics while in the bloodstream or before they are in the bloodstream.

Claim 1 recites the limitations "the bloodstream" (line 2) and "the repair" (line 3). There is insufficient antecedent basis for this limitation in the claim.

Claim 3 recites "method as claimed in claim 1, including any microorganisms ...". It is unclear how or in what way the method of claim 1 includes "any microorganisms".

Claim 6 refers to "rupture of cells." There is a lack of antecedent basis for "rupture" in claim 6. Furthermore, it is unclear which "cells" are being referred to. Claim 1 recites bacteria, which are cells, and cancer cells.

Claim 7 recites "method as claimed in claim 1, including unenclosed (naked) DNA/RNA ...". It is unclear how or in what way the method of claim 1 includes "unenclosed (naked) DNA/RNA", etc.

Claims 9, 13, and 18 recite various means of introducing bacteria into a patient's bloodstream, such as by injection. Three of these are recited as "subcutaneous, intra-muscular, and intra-abdominal". These terms are adjectives, not nouns, and it is unclear what they refer to in the context of the claims.

Claims 12 and 18 recite the limitation ""the DNA/RNA-containing microorganism cells" in lines 9-10 of claim 12 and lines 13-14 of claim 18. There is insufficient antecedent basis for this limitation in the claim. Not all microorganisms are cells, e.g. viruses.

***Double Patenting***

Applicant is advised that should claims 1, 9, 12, and 13 be found allowable, claims 2, 19, 14, and 18, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Applicant is advised that should claim 8 be found allowable, claims 10 and 16 will be objected to under 37 CFR 1.75 as being a substantial duplicates thereof. Applicant is advised that should claim 12 be found allowable, claim 14 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Applicant is advised that should claim 18 be found allowable, claim 14 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 2 recites "including the spillage of other components." Since claim 1 requires killing of the bacteria by antibiotics and spilling of their DNA/RNA, such spilling must also include spillage of other bacterial components as well. Claims 10 and 14 simply reiterate the limitation in claims 8 and 12, respectively, that the intracellular components of the bacteria of microorganism include DNA/RNA. Claims 16, 18, and 19 are literal duplicates of claims 8, 13 and 9, respectively.

***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The claims have not been rejected over prior art since the prior art cannot meet the

inoperative limitation that the method work by repair of broken or damaged DNA in cells of a patient with bacterial DNA. However, the use of live or killed bacteria to treat cancer is not new.

Reports of intentionally causing bacterial infection for the treatment of cancer date back as early as 1752 by applying a septic dressing to a patient with an ulcerated malignant breast, deliberately leaving surgical wounds from removal of a cancer exposed to air to establish a suppurating infection, injecting cancer patients with malaria or syphilis, treating breast cancer by inoculation with clostridia bacteria or spores to cause gas gangrene in a tumor, and causing erysipelas (skin infection caused by *Streptococcus pyogenes*) to treat sarcomas. See Cann et al., Med. Hypoth. 58(2): 115-119, Feb. 2002; Hobohm, U., Cancer Immunol. Immunother. 50(8): 391-396, Oct. 2001; and Pawelek et al. Lancet Oncol. 4(9): 548-556, Sep. 2003. Frequent and long-term administration of heat killed pyrogenic bacteria, primarily *S. pyogenes* and *Serratia marcescens,* to induce a pyrogenic immune response in cancer patients was pioneered by W.B. Coley in the late 1800's and early 1900's (Nauts et al., Adv. Exp. Med. Biol. 267: 483-500, 1990). Mutai et al. (US 4347,240) describes treating cancer by injection of a strain of *Lactobacillus casei*, a non-pathogenic bacteria, to stimulate the immune system. Tjuvajev et al. (J. Control. Release 74 (1-3): 313-315, Jul 2001) and Bermudes et al. (US 6447,784) describe treating a variety of cancers using live attenuated strains of *Salmonella typhimurium*, which preferentially accumulate and reproduce in hypoxic tumors, including the use of strains genetically engineered to express enzymes to convert non-toxic prodrugs into their toxic chemotherapeutic. The actual mechanism for the therapeutic effects of administration of live or dead pyrogenic bacteria is unknown, but is predominately thought to be due to the pyrogenic immune response, either due to hyperthermia (high fever) or to a non-specific stimulation of the

immune system leading to an immune attack on cancer cells or both, (see for example, Nauts, pages 491-492, and Hobohm, pages 394-395).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1633